



# Diagnosis and Treatment of Nontuberculous Mycobacterial Lung Disease

Yong-Soo Kwon<sup>1</sup> and Won-Jung Koh<sup>2</sup>

<sup>1</sup>Department of Internal Medicine, Chonnam National University Hospital, Gwangju, Korea;

<sup>2</sup>Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Received: 24 October 2015

Accepted: 1 February 2016

Address for Correspondence:

Won-Jung Koh, MD

Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea  
E-mail: wjkoh@skku.edu

Funding: This study was funded by the Medical Research Fund of Samsung Medical Center (SMO1140221).

Nontuberculous mycobacteria (NTM) are ubiquitous organisms; their isolation from clinical specimens does not always indicate clinical disease. The incidence of NTM lung diseases has been increasing worldwide. Although the geographic diversity of NTM species is well known, *Mycobacterium avium* complex (MAC), *M. abscessus* complex (MABC), and *M. kansasii* are the most commonly encountered and important etiologic organisms. Two distinct types of NTM lung diseases have been reported, namely fibrocavitary and nodular bronchiectatic forms. For laboratory diagnosis of NTM lung diseases, both liquid and solid media cultures and species-level identification are strongly recommended to enhance growth detection and determine the clinical relevance of isolates. Treatment for NTM lung diseases consists of a multidrug regimen and a long course of therapy, lasting more than 12 months after negative sputum conversion. For MAC lung disease, several new macrolide-based regimens are now recommended. For nodular bronchiectatic forms of MAC lung diseases, an intermittent three-time-weekly regimen produces outcomes similar to those of daily therapy. Treatment of MABC lung disease is very difficult, requiring long-term use of parenteral agents in combination with new macrolides. Treatment outcomes are much better for *M. massiliense* lung disease than for *M. abscessus* lung disease. Thus, precise identification of species in MABC infection is needed for the prediction of antibiotic response. Likewise, increased efforts to improve treatment outcomes and develop new agents for NTM lung disease are needed.

**Keywords:** Nontuberculous Mycobacteria; *Mycobacterium avium* Complex; *Mycobacterium abscessus*; *Mycobacterium kansasii*

## INTRODUCTION

The term, nontuberculous mycobacteria (NTM), generally refers to mycobacteria other than *Mycobacterium tuberculosis* complex and *M. leprae* (1). NTM are ubiquitous organisms commonly isolated from environments such as drinking water, natural water, and soil (2). Host factors, such as genetic susceptibility, immune defects, and structural lung disease, as well as environmental factors, including humidity, altitude, and shower systems may also influence the development of NTM lung diseases (1,3,4).

NTM can be divided into two groups based on their rate of growth on solid culture medium. For slowly growing mycobacteria, visible colonies are produced after 7 days, compared to within 7 days for rapidly growing mycobacteria. Slowly growing mycobacteria include *M. avium* complex (MAC) and *M. kansasii*, whereas rapidly growing mycobacteria include *M. abscessus* complex (MABC) (1).

The incidence and prevalence of NTM lung diseases are increasing worldwide, and they can affect both immunocompetent and immunocompromised individuals (5). In Korea, NTM

lung disease was first reported in 1981 (6), and the frequency of NTM isolations from clinical specimens, and the numbers of patients with NTM lung diseases, have been increasing over recent decades (7). Given these trends, clinicians should be aware of this disease. In this article, we review the epidemiology and the clinical and radiological manifestations of NTM lung disease, as well as relevant laboratory diagnosis parameters and treatment regimens.

## EPIDEMIOLOGY

The incidence of NTM lung disease is increasing worldwide. Specifically, increasing incidence and prevalence of NTM lung disease has been reported in many countries, including western countries such as the United States (8), Canada (9), and the United Kingdom (10), as well as Asian countries like Japan (11) and Taiwan (12).

Although there has been no population-based epidemiologic study on NTM lung disease in Korea, the proportion of NTM among positive mycobacterial cultures is increasing in many hospitals. Before the early 1990s, 97%-98% of mycobacterial iso-

lates from sputum specimens contained *M. tuberculosis* (7). However, after the early 2000s, NTM were isolated from 20%-30% of all clinical specimens submitted to mycobacterial laboratories in many referral hospitals, and this rate further increased, to approximately 50%-70%, in the early 2010s in Korea (13-17) (Table 1).

The geographic diversity of NTM species in clinical specimens is well known. A recent study analyzed NTM isolates from respiratory specimens of 20,182 patients from 62 laboratories in 30 countries across six continents (18). Across all regions, the most common NTM species is MAC, followed by *M. goodii*, *M. xenopi*, and *M. kansasii*. Among rapid growers, MABC and *M. fortuitum* are the most commonly isolated species worldwide. However, NTM species distribution varies by region and country (18). Although MAC is the most common species in Asia as a whole, the prevalence of MABC is higher in some Asian countries, including Korea (18).

As in other countries, MAC is the most common etiologic organism (about 60%-70%) in NTM lung disease in Korea (13,14,19,20) (Table 2). While *M. intracellulare* has been more prevalent than *M. avium* in MAC lung disease in the past few years (19), *M. avium* has been isolated more frequently in recent years (14,21). Because of advances in molecular techniques, new species have been discovered in MAC. *M. chimaera* is one such novel species associated with MAC, and a recent study from the United States showed that about 20% of MAC lung disease is caused by *M. chimaera* (22). However, the proportion of *M. chimaera* in MAC lung disease in Korea is unknown. MABC is the second most common etiologic organism (about 20%-30%) in NTM lung disease in Korea (Table 2). Within MABC in Korea,

*M. abscessus* (44%-53%) and *M. massiliense* (45%-55%) are equally distributed, while *M. bolletii* is a relatively rare pathogen (1%-2%) (23-26). In addition, *M. kansasii* is infrequently isolated, and remains a relatively uncommon cause of NTM lung disease in Korea (27-29) (Table 2).

Geographic differences in the prevalence and distribution of bacterial species in NTM lung disease might be due to a combination of environmental and host immune and behavioral factors. However, environmental risk factors remain poorly understood. For example, one study reported the predominance of NTM in showerheads and the presence of MAC in nearly one-third of shower biofilm samples collected around the United States (30). Another study suggested that specific environmental factors, such as high mean daily potential evapotranspiration levels and percentage of surface water, are associated with increased incidence of NTM lung disease (4). A study of a registry of cystic fibrosis patients reported that high saturated vapor pressure is related to increased prevalence of NTM lung disease (31). The results of this study suggest that high-moisture environments might lead to large numbers of circulating aerosolized mycobacteria and an increased risk of NTM infection in patients with cystic fibrosis (31). Thus, regions with higher vapor pressure and temperatures may have an increased prevalence of NTM lung disease.

NTM disease is also an important cause of disease in immunocompromised hosts (32,33), which includes patients with human immunodeficiency virus infection, malignancy, and autoimmune disease, particularly those receiving tumor necrosis factor (TNF)- $\alpha$  blockers. Interestingly, studies from the Unit-

**Table 1.** Increasing proportions of nontuberculous mycobacteria of all positive mycobacterial cultures from respiratory clinical specimens in Korea

Author, year	Hospital	Study period	Proportion of NTM in clinical isolates	
			Start of study period	End of study period
Park et al., 2010 (13)	Seoul National University Hospital	2002-2008	427/1,921 (22%)	781/1,701 (46%)
Lee et al., 2012 (14)	Severance Hospital	2006-2010	268/1,041 (26%)	970/2,064 (47%)
Yoo et al., 2012 (15)	Asan Medical Center	2002-2010	403/1,921 (21%)	1,530/2,648 (59%)
Koh et al., 2013 (16)	Samsung Medical Center	2001-2011	548/1,283 (43%)	3,341/4,800 (70%)
Kim et al., 2013 (17)	Dankook University Hospital	2005-2011	26%	44%

**Table 2.** Common etiologic organism in patients with nontuberculous mycobacterial lung disease in Korea

Author, year	Koh et al., 2006 (19)	Park et al., 2010 (13)	Lee et al., 2012 (14)	Jang et al., 2014 (20)
Study period	2002-2003	2002-2008	2006-2010	2012
No. of patients	195	651	345	111
<i>M. avium</i> complex	94 (48%)	63%	263 (76%)	73 (66%)
<i>M. avium</i>	38	NA	141	32
<i>M. intracellulare</i>	56	NA	122	41
<i>M. abscessus</i> complex	64 (33%)	27%	63 (18%)	32 (29%)
<i>M. abscessus</i>	NA	NA	NA	21
<i>M. massiliense</i>	NA	NA	NA	11
<i>M. kansasii</i>	7 (4%)	NA	7 (2%)	1 (1%)
Others	30 (15%)	10%	12 (3%)	5 (5%)

NA, not available.

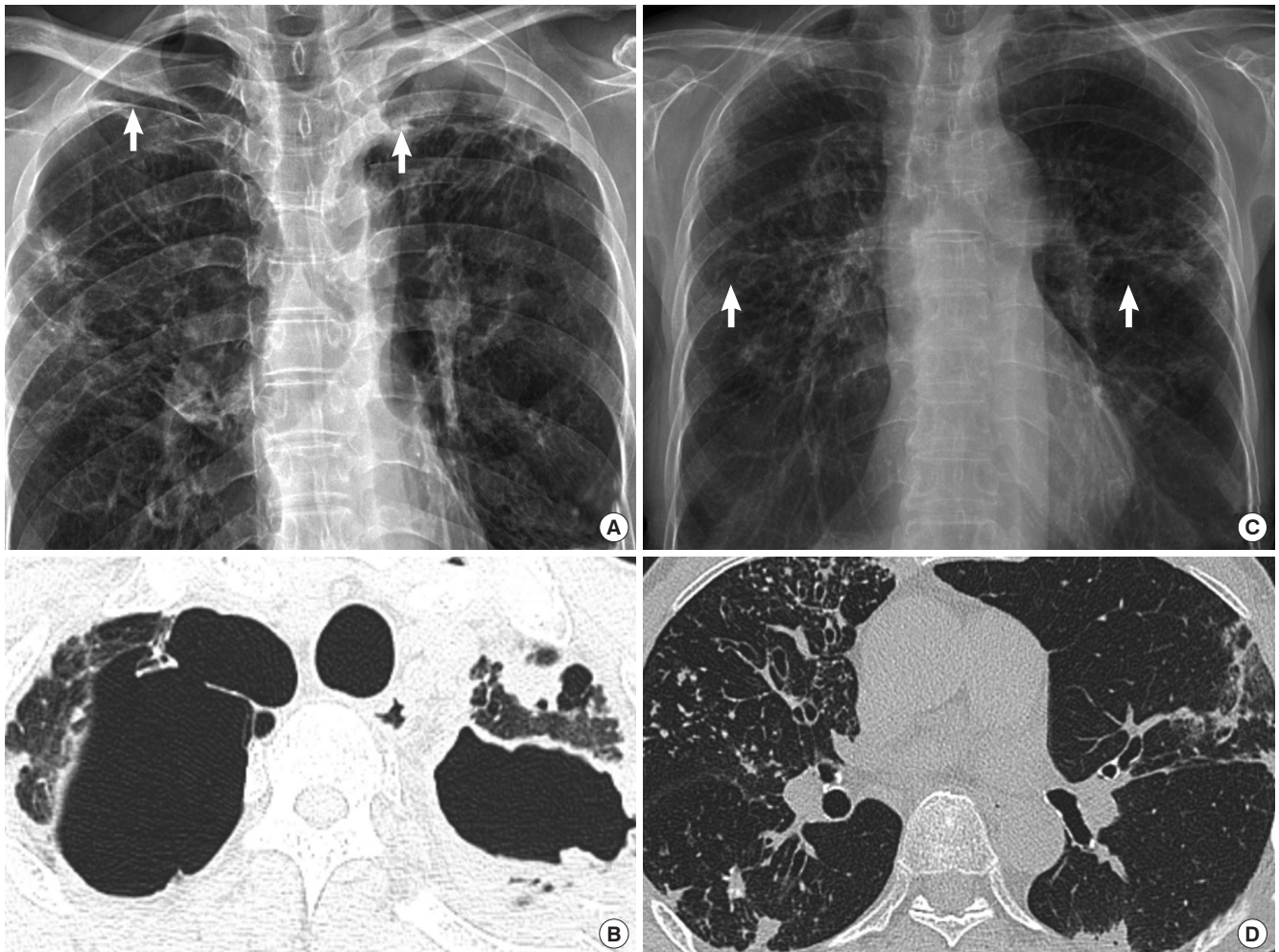
ed States and Canada revealed that the use of TNF- $\alpha$  blockers is associated with an increased risk of both tuberculosis (TB) and NTM disease (34,35). Similar findings have also been reported in Korea (36,37).

### CLINICAL AND RADIOLOGICAL MANIFESTATIONS

Pulmonary TB remains a major health concern, and the number of reported TB cases in Korea has not significantly decreased over the last decade (38-40). Therefore, differentiating between pulmonary TB and NTM lung disease is important for controlling TB transmission and preventing unnecessary TB treatment in patients with NTM lung disease (41). The symptoms of NTM lung disease – cough, sputum, hemoptysis, fatigue, malaise, and weight loss – are nonspecific and similar to symptoms of pulmonary TB, and thus may also reflect underlying lung disease such as bronchiectasis and chronic obstructive lung dis-

ease. Patients with NTM lung disease are more likely to be older, female, non-smoking, and to have fewer constitutional symptoms, a history of previous TB treatment, absence of pleural effusion, involvement of the middle and lower lung zone, and bilateral disease than do patients with pulmonary TB. However, there is considerable overlap in the clinical and radiographic findings between the two conditions (42,43). Therefore, additional microbiologic diagnostics are essential.

NTM lung disease has two different radiographic manifestations: fibrocavitary and nodular bronchiectatic forms (44,45). Fibrocavitary forms of NTM lung disease have cavitory lesions predominantly in the upper lobes, with radiographic findings are similar to those of pulmonary TB (1) (Fig. 1A and B). This manifestation shows relatively rapid disease progression and frequently develops in older men with a history of smoking and underlying lung disease such as previous TB (1). The other form of NTM lung disease is nodular bronchiectatic disease. This



**Fig. 1.** Two distinct manifestations of nontuberculous mycobacterial lung disease: fibrocavitary and nodular bronchiectatic forms. (A, B) A 56-year-old male with *Mycobacterium avium* lung disease. The chest radiograph shows cavities in both upper lung fields. The chest CT shows two thin walled cavities in bilateral upper lobes. (C, D) An 83-year-old female with *Mycobacterium avium* lung disease. The chest radiograph shows multiple nodules in both mid-lung fields. The chest CT shows multiple centrilobular nodules with bronchiectasis in the right middle lobe and the lingular segment of the left upper lobe.



**Table 3.** Diagnostic criteria for nontuberculous mycobacterial lung disease\*

Clinical (both required)
1. Pulmonary symptoms, nodular or cavitory opacities on chest radiograph, or a high-resolution computed tomography scan that shows multifocal bronchiectasis with multiple small nodules
AND
2. Appropriate exclusion of other diagnoses
Microbiologic
1. Positive culture results from at least two separate expectorated sputum samples. If the results from the initial sputum samples are nondiagnostic, consider repeat sputum AFB smears and cultures
OR
2. Positive culture result from at least one bronchial wash or lavage
OR
3. Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM
4. Expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination.
5. Patients who are suspected of having NTM lung disease but do not meet the diagnostic criteria should be followed until the diagnosis is firmly established or excluded.
6. Making the diagnosis of NTM lung disease does not, per se, necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients

AFB, acid-fast bacilli; NTM, nontuberculous mycobacteria.

\*Reproduced with permission of the American Thoracic Society. Copyright © 2015 American Thoracic Society (1).

manifestation can present as multifocal bronchiectasis, clusters of small nodules, and branching linear structures that frequently involve the right middle lobe and the lingular segment of the left upper lobe (46,47) (Fig. 1C and D). Although these findings are quite specific for NTM lung disease, particularly MAC and MABC infections, other diseases such as diffuse panbronchiolitis may present with similar findings (48,49). In the nodular bronchiectatic form of NTM lung disease, patients have unique body morphotypes, including a lower body mass index and body fat, taller stature, and increased instances of scoliosis and pectus excavatum, compared to control subjects (50-52).

Uncommon presentations of NTM lung disease include hypersensitivity-like disease and solitary pulmonary nodules. Hypersensitivity-like disease, also known as “hot tub lung,” has been reported in relation to aerosols of infected water, including household water, medicinal baths, pools, hot tubs, and occupational exposure such as from metal-working fluids and fisheries (53,54). Hypersensitivity-like disease is similar to hypersensitivity pneumonitis with respect to its clinical and radiologic presentation. Another uncommon presentation is solitary pulmonary nodules. In TB-prevalent areas, solitary pulmonary nodules with granulomatous inflammation in histological examinations are generally considered to indicate tuberculoma, and TB drugs are administered for treatment. However, solitary pulmonary nodules caused by NTM cannot be differentiated from tuberculoma by clinical, radiographic, or even pathologic examination (55,56). Therefore, physicians should consider the possibility of solitary pulmonary nodules caused by NTM to prevent unnecessary treatment with long-duration TB drugs.

Clinical and microbiological criteria from the American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA) are widely used to diagnose NTM lung disease (1). Clinical findings should include pulmonary symptoms and com-

patible radiographic evidence (nodular or cavitory opacities) and high-resolution computed tomography findings (multifocal bronchiectasis with multiple small nodules). Microbiological criteria include two positive sputum cultures, one positive bronchial wash or lavage, or compatible mycobacterial histological features such as granulomatous inflammation, positive acid-fast bacilli (AFB) lung biopsy, positive lung biopsy culture, or more than one positive sputum culture or bronchial wash (1) (Table 3). These criteria fit best with MAC, MABC, and *M. kansasii*; however, there is insufficient information regarding other forms of NTM to be certain that these diagnostic criteria are universally applicable for all types of NTM respiratory pathogens (1).

## LABORATORY DIAGNOSIS

Smear microscopy is an inexpensive method for rapid detection of mycobacteria; however, it cannot differentiate NTM from *M. tuberculosis* (57). Therefore, detection of mycobacterial growth in culture media is necessary for definite diagnosis of NTM lung disease, although this method requires several weeks before results can be obtained. Nucleic acid amplification (NAA) assays are an excellent tool for rapid detection of *M. tuberculosis* directly from clinical specimens, offering higher sensitivity than smear microscopy (58,59). The test can also rapidly discriminate between *M. tuberculosis* and NTM in smear-positive specimens (60). If the AFB smear result is positive and the NAA result is negative, the patient can be presumed to have NTM lung disease (41). Thus, NAA tests can be used as an additional test for patients with AFB smear-positive sputum for the rapid detection of *M. tuberculosis* and differentiation from NTM. In addition, some commercial tests are currently available that amplify different target genes to detect *M. tuberculosis* and several NTM

species (61,62).

Both liquid and solid media are recommended for mycobacterial culture to enhance the ability to detect growth of *M. tuberculosis* and NTM (63). Increased growth in both liquid and solid culture media is more prominent for NTM than for *M. tuberculosis*, especially in smear-negative respiratory specimens (64). In addition, culturing allows for the identification of NTM species, drug susceptibility tests, and genotyping of particular NTM species, and helps to assess treatment response using semi-quantitative results in solid media (65).

Identification of NTM species is very important, due to differences in clinical relevance of NTM isolates and drug susceptibilities that require different antibiotic treatment regimens. For this reason, species-level identification of NTM is recommended (64). The methods for identifying mycobacteria in clinical laboratories have changed dramatically over the past two decades. Specifically, molecular methods have now surpassed biochemical tests and high-performance liquid chromatography (HPLC) as the methods of choice for NTM identification (64). Among molecular methods, polymerase chain reaction (PCR) and restriction fragment length polymorphism analysis or PCR-reverse blot hybridization assay of the *rpoB* gene have been developed for use in clinical practice in Korea (41). For precise subspecies-level identification of MABC and uncommon species, sequencing of the *hsp65* and *rpoB* genes and the 16S-23S rRNA internal transcribed spacer (ITS) region is necessary (64).

The utility of in vitro susceptibility tests for managing patients with NTM remains controversial (1). Macrolides play a key role in MAC treatment, and in vitro clarithromycin susceptibility testing is recommended for both new and previously untreated patients as well as those who fail to respond to macrolide treatment for MAC lung disease (1). Clarithromycin is recommended as the class agent for testing macrolides because clarithromycin and azithromycin share cross-resistance and similar patterns of organism susceptibility. Previously untreated *M. kansasii* strains should be tested in vitro only with rifampin. *M. kansasii* isolates resistant to rifampin should be tested against a panel of secondary agents, including rifabutin, ethambutol, isoniazid, clarithromycin, fluoroquinolones, amikacin, and sulfonamides (1). For MABC, drug susceptibility testing is difficult and of controversial merit (66). Current guidelines recommend susceptibility testing against a panel of drugs, including amikacin, cefoxitin, clarithromycin, ciprofloxacin, doxycycline, imipenem, linezolid, moxifloxacin, trimethoprim-sulfamethoxazole and tobramycin, although there is limited evidence on the applicability of the results of in vitro tests of susceptibility to the clinical response to treatment regimens based on those tests (1). With respect to in vitro susceptibility testing, MABC is typically susceptible to amikacin, cefoxitin, and clarithromycin. Macrolides are frequently the only oral agents active against

MABC, and there is correlation between in vitro susceptibility and treatment response (67). However, inducible macrolide resistance was recently discovered in *M. abscessus*, with altered resistance to clarithromycin observed during in vitro susceptibility testing after prolonged incubation (susceptible at day 3 but resistant at day 14) or pre-incubation in macrolide-containing media (68). This inducible resistance to clarithromycin is due to a functioning erythromycin ribosomal methylase gene, *erm* (41), which is present in most strains of *M. abscessus*, but not in *M. massiliense* (69-71).

## TREATMENT

Treatment of NTM lung disease is difficult due to the uncertainty surrounding the timing of when treatment should be started and which regimen is most likely to achieve a successful treatment (1). Initiation of NTM treatment should be individualized considering disease types, comorbid conditions, and age. Patients with fibrocavitary disease usually require immediate treatment, because the presence of cavitary disease is associated with higher mortality (72,73). On the other hand, nodular bronchiectatic disease tends to occur in the absence of significant comorbidity and progresses very slowly (46). Therefore, early treatment of mild and indolent nodular bronchiectatic disease may not be advisable, due to adverse drug effects from the long-term use of many drugs (1). These decisions may also be aided by molecular analyses, as specific mycobacterial genotypes within the same species have been shown to predict disease progression or treatment response in patients with NTM lung disease (74,75).

### *Mycobacterium avium* complex lung disease

Newer macrolide drugs such as azithromycin and clarithromycin are the cornerstone of MAC treatment. Specifically, current guidelines for the treatment of MAC lung disease recommend a three-drug macrolide-based therapy including macrolides, rifampin, and ethambutol (Table 4) (1). In addition, streptomycin is recommended for patients with severe and advanced disease, especially if of fibrocavitary form (1). Antibiotic therapy should be continued for at least 12 months after the conversion of sputum cultures from positive to negative. In non-cavitary nodular bronchiectatic MAC lung disease, intermittent, three-times-weekly therapy is recommended over daily therapy to improve drug tolerability (Table 4) (1). Importantly, intermittent therapy has potential benefits in decreasing adverse drug effects and medication costs, as well as in increasing treatment compliance (76,77).

Despite advances in understanding treatment regimens and therapeutics, overall, treatment outcomes remain unsatisfactory. Specifically, patient dropout rates are 10%-30% due to adverse drug effects, and treatment success rates are only 40%-

**Table 4.** Treatment regimen for nontuberculous mycobacterial lung disease

NTM species	Drug regimens	Duration of therapy
<i>Mycobacterium avium</i> complex	Non-cavitary nodular bronchiectatic form; clarithromycin 1,000 mg or azithromycin 500 mg TIW plus ethambutol 25 mg/kg TIW plus rifampin 600 mg TIW	12 mon of negative sputum conversion
	Fibrocavitary form or cavitary nodular bronchiectatic form; clarithromycin 1,000 mg or azithromycin 250 mg daily plus ethambutol 15 mg/kg daily plus rifampin 450-600 mg daily plus and/or streptomycin 10-15 mg/kg IM TIW or amikacin 10-15 mg/kg IV TIW	12 mon of negative sputum conversion
<i>Mycobacterium abscessus</i> complex	amikacin 10-15 mg/kg IV daily plus cefoxitin up to 12 g IV or imipenem 1,000-2,000 mg IV daily plus clarithromycin 1,000 mg or azithromycin 250 mg daily	12 mon of negative sputum conversion
<i>Mycobacterium kansasii</i>	isoniazid 5 mg/kg daily up to 300 mg daily plus rifampin 10 mg/kg daily up to 600 mg daily plus ethambutol 15 mg/kg daily or clarithromycin 1,000 mg or azithromycin 250 mg daily rifampin 10 mg/kg daily up to 600 mg daily plus ethambutol 15 mg/kg daily	12 mon of negative sputum conversion

TIW, three times weekly; IM, intramuscular; IV, intravenous.

60% (78,79). Furthermore, even after successful completion of antibiotic therapy, microbiologic recurrence is relatively common, mainly due to MAC reinfection (76,80,81). Indeed, prolonged duration of treatment, drug side effects, and reinfection rather than relapse are responsible for the suboptimal treatment success rates of MAC lung disease.

Drug-drug interactions, especially those between rifampin and macrolides, can cause reduced plasma concentrations of macrolides, resulting in suboptimal responses to antibiotic treatment for MAC lung disease. Specifically, low serum concentrations of macrolides caused by drug-drug interactions are very common in patients treated for MAC lung disease with regimens consisting of both clarithromycin and rifampin (82,83). However, it remains unclear whether low serum concentrations of macrolides are the reason for suboptimal treatment outcomes, and whether increasing the dose of macrolide or substituting rifampin for another drug can improve treatment outcomes for MAC lung disease.

Although there have been many studies aimed at improving treatment outcomes for MAC lung disease, and current guidelines recommend evidence-based standard treatments for this disease, current treatment outcomes remain unsatisfactory. Furthermore, the recommended regimens are associated with numerous side effects due to the use of multiple drugs and the long duration of treatment. As a result, clinician adherence to guidelines may not be very high, further contributing to poor treatment outcomes (84). Indeed, in a survey of United States physicians treating patients with MAC lung disease regarding adherence to guidelines, only 13% of the antibiotic regimens prescribed to patients with MAC met current guidelines, while 30% of the prescribed regimens were associated with an increased risk of developing macrolide resistance (84). In treating

MAC lung disease, preventing the emergence of macrolide resistance is very important. Specifically, development of macrolide resistance is strongly associated with treatment failure and increased mortality (85). The most important risk factors for developing macrolide-resistant MAC are macrolide monotherapy and the combination of macrolides and fluoroquinolone without a third companion drug (85).

The value of adding additional drugs to standard antibiotic treatment of refractory MAC lung disease is unclear (86). A study suggested that clofazimine with clarithromycin and ethambutol is as effective as currently-recommended macrolide-rifampin-ethambutol therapy (87). Moxifloxacin may improve treatment outcomes in about one-third of patients with persistently culture-positive MAC lung disease who fail to respond to standardized antibiotic treatment (88). However, the role of these agents in treating refractory MAC lung disease remains unclear (86).

Although species differentiation between *M. intracellulare* and *M. avium* in terms of clinical features and prognosis were not clearly defined therein, a recent large retrospective cohort study showed that patients with *M. intracellulare* lung disease present more severe manifestations: lower body mass index, more frequent presence of respiratory symptoms and fibrocavitary disease, higher rate of smear-positive sputum, and worse prognosis, including more frequent initiation of antibiotic treatment during follow-up period and higher unfavorable treatment response than those in patients with *M. avium* lung disease (21). The same group also reported that patients with *M. intracellulare* lung disease showed evidence of more extensive disease in chest CT scan than did patients with *M. avium* lung disease (47).

### ***Mycobacterium abscessus* complex lung disease**

The treatment of MABC lung disease is more difficult than that of MAC lung disease due to a lack of effective antibiotics. MABC is resistant to many antibiotics and is only susceptible in vitro to the parenteral agents, amikacin, cefoxitin, and imipenem, and to the oral macrolides, clarithromycin and azithromycin (1). Therefore, current guidelines recommend a regimen consisting of two parenteral agents and a macrolide for 2 to 4 months (Table 2) (1). However, there is little data on the efficacy and safety of this regimen, and its high cost and numerous side effects may limit its use. Several studies regarding treatment outcome in MABC lung disease have recently been reported, with positive results ranging from 25% to 88% (24,67,89-91). However, these were retrospective studies utilizing various regimens with different treatment durations, and many patients included in these studies received treatment in combination with surgery. Therefore, the results of these studies may not be generalizable to all patients, and should be interpreted cautiously with respect to treating individuals with MABC lung disease.

A recent study differentiated MABC lung disease according to causative organism, including *M. abscessus*, *M. massiliense*, and *M. bolletii* (92), although the taxonomic status of MABC is still a matter of debate (93). The precise differentiation of the etiologic organisms is very important due to the high treatment success rate in *M. massiliense* lung disease compared to that in *M. abscessus* lung disease. In a recent study on this issue, negative culture conversion was achieved and maintained in 88% of patients with *M. massiliense* lung disease, which was significantly higher than that with *M. abscessus* lung disease (25%) (24). Similar results have been reported in other studies (91,94,95).

There are currently no standard antibiotic strategies for MABC lung disease, nor are there any highly effective and safe antibiotics. For these reasons, experts believe that curative therapy for MABC lung disease may only be feasible in patients with limited disease and in combination with surgical resection and chemotherapy (90,96). On the other hand, suppressive therapy using periodic parenteral antibiotics or oral antibiotics to control symptoms and progression of disease may be appropriate for the majority of patients. Recently, new treatment options for MABC lung disease have been investigated, including amikacin inhalation treatment and the novel drug bedaquiline (97-99). In a preliminary study on refractory MABC lung disease, both amikacin inhalation and bedaquiline therapy, in addition to other drugs, showed encouraging results (97,99). A liposomal form of amikacin inhalation therapy is currently under study for treatment of this disease (www.clinicaltrials.gov, identifier NCT01315236).

### ***Mycobacterium kansasii* lung disease**

Rifampin is the most important drug in the treatment of *M. kansasii* lung disease due to the high culture conversion rate and

low long-term relapse rate that follow drug introduction (1). Current guidelines recommend a rifampin-containing regimen in combination with isoniazid and ethambutol (Table 2) (1). This regimen is associated with a high sputum culture conversion rate and low long-term recurrence rate. In a study in Korea, the sputum culture conversion rate with rifampin-based regimens was very high, reaching 95% in patients who received antibiotic therapy for more than 12 months (28), the recommended duration of treatment after negative sputum conversion. In these cases, because antibiotic therapy produces an excellent treatment outcome, surgical resection is not recommended to treat the disease. In addition, due to the high efficacy of new macrolides against *M. kansasii* and the questionable role of isoniazid in the current recommended regimen, some experts are now recommending substituting macrolides for isoniazid (100).

## **CONCLUSIONS**

The incidence of NTM lung disease is increasing worldwide. In addition, NTM species exhibit significant geographic diversity. MAC and MABC are the most commonly encountered etiologic organisms in NTM lung disease. There are two distinctive types of NTM lung disease, namely nodular bronchiectatic and fibrocavitary forms. Precise species-level identification of NTM is very important due to species-based differences in treatment regimen and prognosis. Treatment of NTM lung disease requires multiple drugs over a long course of therapy. However, treatment outcomes are routinely unsatisfactory. Thus, additional efforts to improve treatment outcome and develop new agents for NTM lung disease treatment are needed.

## **DISCLOSURE**

The authors have no potential conflicts of interest to disclose.

## **AUTHOR CONTRIBUTION**

Both authors contributed to the conception and design of the research, and to the writing and revision of the manuscript.

## **ORCID**

Yong-Soo Kwon <http://orcid.org/0000-0001-5121-4488>

Won-Jung Koh <http://orcid.org/0000-0002-4756-3527>

## **REFERENCES**

1. Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, Holland SM, Horsburgh R, Huitt G, Iademarco MF, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007; 175: 367-416.



2. Falkinham JO 3rd. Environmental sources of nontuberculous mycobacteria. *Clin Chest Med* 2015; 36: 35-41.
3. Szymanski EP, Leung JM, Fowler CJ, Haney C, Hsu AP, Chen F, Duggal P, Oler AJ, McCormack R, Podack E, et al. Pulmonary nontuberculous mycobacterial infection. A multisystem, multigenic disease. *Am J Respir Crit Care Med* 2015; 192: 618-28.
4. Adjemian J, Olivier KN, Seitz AE, Falkinham JO 3rd, Holland SM, Prevots DR. Spatial clusters of nontuberculous mycobacterial lung disease in the United States. *Am J Respir Crit Care Med* 2012; 186: 553-8.
5. Prevots DR, Marras TK. Epidemiology of human pulmonary infection with nontuberculous mycobacteria: a review. *Clin Chest Med* 2015; 36: 13-34.
6. Kim SJ, Hong YP, Kim SC, Bai GH, Jin BW, Park CD. A case of pulmonary disease due to *Mycobacterium avium*-intracellulare complex. *Tuberc Respir Dis (Seoul)* 1981; 28: 121-4.
7. Koh WJ, Kwon OJ, Lee KS. Diagnosis and treatment of nontuberculous mycobacterial pulmonary diseases: a Korean perspective. *J Korean Med Sci* 2005; 20: 913-25.
8. Adjemian J, Olivier KN, Seitz AE, Holland SM, Prevots DR. Prevalence of nontuberculous mycobacterial lung disease in U.S. Medicare beneficiaries. *Am J Respir Crit Care Med* 2012; 185: 881-6.
9. Marras TK, Mendelson D, Marchand-Austin A, May K, Jamieson FB. Pulmonary nontuberculous mycobacterial disease, Ontario, Canada, 1998-2010. *Emerg Infect Dis* 2013; 19: 1889-91.
10. Moore JE, Kruijshaar ME, Ormerod LP, Drobniewski F, Abubakar I. Increasing reports of non-tuberculous mycobacteria in England, Wales and Northern Ireland, 1995-2006. *BMC Public Health* 2010; 10: 612.
11. Ide S, Nakamura S, Yamamoto Y, Kohno Y, Fukuda Y, Ikeda H, Sasaki E, Yanagihara K, Higashiyama Y, Hashiguchi K, et al. Epidemiology and clinical features of pulmonary nontuberculous mycobacteriosis in Nagasaki, Japan. *PLoS One* 2015; 10: e0128304.
12. Chien JY, Lai CC, Sheng WH, Yu CJ, Hsueh PR. Pulmonary infection and colonization with nontuberculous mycobacteria, Taiwan, 2000-2012. *Emerg Infect Dis* 2014; 20: 1382-5.
13. Park YS, Lee CH, Lee SM, Yang SC, Yoo CG, Kim YW, Han SK, Shim YS, Yim JJ. Rapid increase of non-tuberculous mycobacterial lung diseases at a tertiary referral hospital in South Korea. *Int J Tuberc Lung Dis* 2010; 14: 1069-71.
14. Lee SK, Lee EJ, Kim SK, Chang J, Jeong SH, Kang YA. Changing epidemiology of nontuberculous mycobacterial lung disease in South Korea. *Scand J Infect Dis* 2012; 44: 733-8.
15. Yoo JW, Jo KW, Kim MN, Lee SD, Kim WS, Kim DS, Shim TS. Increasing trend of isolation of non-tuberculous mycobacteria in a tertiary university hospital in South Korea. *Tuberc Respir Dis (Seoul)* 2012; 72: 409-15.
16. Koh WJ, Chang B, Jeong BH, Jeon K, Kim SY, Lee NY, Ki CS, Kwon OJ. Increasing recovery of nontuberculous mycobacteria from respiratory specimens over a 10-year period in a tertiary referral hospital in South Korea. *Tuberc Respir Dis (Seoul)* 2013; 75: 199-204.
17. Kim JK, Rheem I. Identification and distribution of nontuberculous mycobacteria from 2005 to 2011 in Cheonan, Korea. *Tuberc Respir Dis (Seoul)* 2013; 74: 215-21.
18. Hoefsloot W, van Ingen J, Andrejak C, Angeby K, Bauriaud R, Bemer P, Beylis N, Boeree MJ, Cacho J, Chihota V, et al. The geographic diversity of nontuberculous mycobacteria isolated from pulmonary samples: an NTM-NET collaborative study. *Eur Respir J* 2013; 42: 1604-13.
19. Koh WJ, Kwon OJ, Jeon K, Kim TS, Lee KS, Park YK, Bai GH. Clinical significance of nontuberculous mycobacteria isolated from respiratory specimens in Korea. *Chest* 2006; 129: 341-8.
20. Jang MA, Koh WJ, Huh HJ, Kim SY, Jeon K, Ki CS, Lee NY. Distribution of nontuberculous mycobacteria by multigene sequence-based typing and clinical significance of isolated strains. *J Clin Microbiol* 2014; 52: 1207-12.
21. Koh WJ, Jeong BH, Jeon K, Lee NY, Lee KS, Woo SY, Shin SJ, Kwon OJ. Clinical significance of the differentiation between *Mycobacterium avium* and *Mycobacterium intracellulare* in *M avium* complex lung disease. *Chest* 2012; 142: 1482-8.
22. Boyle DP, Zembower TR, Reddy S, Qi C. Comparison of clinical features, virulence, and relapse among *Mycobacterium avium* complex species. *Am J Respir Crit Care Med* 2015; 191: 1310-7.
23. Kim HY, Kook Y, Yun YJ, Park CG, Lee NY, Shim TS, Kim BJ, Kook YH. Proportions of *Mycobacterium massiliense* and *Mycobacterium bolletii* strains among Korean *Mycobacterium chelonae*-*Mycobacterium abscessus* group isolates. *J Clin Microbiol* 2008; 46: 3384-90.
24. Koh WJ, Jeon K, Lee NY, Kim BJ, Kook YH, Lee SH, Park YK, Kim CK, Shin SJ, Huit GA, et al. Clinical significance of differentiation of *Mycobacterium massiliense* from *Mycobacterium abscessus*. *Am J Respir Crit Care Med* 2011; 183: 405-10.
25. Lee SH, Yoo HK, Kim SH, Koh WJ, Kim CK, Park YK, Kim HJ. The drug resistance profile of *Mycobacterium abscessus* group strains from Korea. *Ann Lab Med* 2014; 34: 31-7.
26. Kim SY, Kim CK, Bae IK, Jeong SH, Yim JJ, Jung JY, Park MS, Kim YS, Kim SK, Chang J, et al. The drug susceptibility profile and inducible resistance to macrolides of *Mycobacterium abscessus* and *Mycobacterium massiliense* in Korea. *Diagn Microbiol Infect Dis* 2015; 81: 107-11.
27. Yim JJ, Park YK, Lew WJ, Bai GH, Han SK, Shim YS. *Mycobacterium kansasii* pulmonary diseases in Korea. *J Korean Med Sci* 2005; 20: 957-60.
28. Park HK, Koh WJ, Shim TS, Kwon OJ. Clinical characteristics and treatment outcomes of *Mycobacterium kansasii* lung disease in Korea. *Yonsei Med J* 2010; 51: 552-6.
29. Moon SM, Park HY, Jeon K, Kim SY, Chung MJ, Huh HJ, Ki CS, Lee NY, Shin SJ, Koh WJ. Clinical significance of *Mycobacterium kansasii* isolates from respiratory specimens. *PLoS One* 2015; 10: e0139621.
30. Feazel LM, Baumgartner LK, Peterson KL, Frank DN, Harris JK, Pace NR. Opportunistic pathogens enriched in showerhead biofilms. *Proc Natl Acad Sci U S A* 2009; 106: 16393-9.
31. Adjemian J, Olivier KN, Prevots DR. Nontuberculous mycobacteria among patients with cystic fibrosis in the United States: screening practices and environmental risk. *Am J Respir Crit Care Med* 2014; 190: 581-6.
32. Henkle E, Winthrop KL. Nontuberculous mycobacteria infections in immunosuppressed hosts. *Clin Chest Med* 2015; 36: 91-9.
33. Park SW, Song JW, Shim TS, Park MS, Lee HL, Uh ST, Park CS, Kim DS. Mycobacterial pulmonary infections in patients with idiopathic pulmonary fibrosis. *J Korean Med Sci* 2012; 27: 896-900.
34. Winthrop KL, Baxter R, Liu L, Varley CD, Curtis JR, Baddley JW, McFarland B, Austin D, Radcliffe L, Suhler E, et al. Mycobacterial diseases and antitumour necrosis factor therapy in USA. *Ann Rheum Dis* 2013; 72: 37-42.
35. Brode SK, Jamieson FB, Ng R, Campitelli MA, Kwong JC, Paterson JM, Li P, Marchand-Austin A, Bombardier C, Marras TK. Increased risk of mycobacterial infections associated with anti-rheumatic medications. *Thorax* 2015; 70: 677-82.



36. Lee SK, Kim SY, Kim EY, Jung JY, Park MS, Kim YS, Kim SK, Chang J, Kang YA. Mycobacterial infections in patients treated with tumor necrosis factor antagonists in South Korea. *Lung* 2013; 191: 565-71.
37. Yoo JW, Jo KW, Kang BH, Kim MY, Yoo B, Lee CK, Kim YG, Yang SK, Byeon JS, Kim KJ, et al. Mycobacterial diseases developed during anti-tumour necrosis factor-alpha therapy. *Eur Respir J* 2014; 44: 1289-95.
38. Park YK, Park YS, Na KI, Cho EH, Shin SS, Kim HJ. Increased tuberculosis burden due to demographic transition in Korea from 2001 to 2010. *Tuberc Respir Dis (Seoul)* 2013; 74: 104-10.
39. Kwon YS, Kim YH, Song JU, Jeon K, Song J, Ryu YJ, Choi JC, Kim HC, Koh WJ. Risk factors for death during pulmonary tuberculosis treatment in Korea: a multicenter retrospective cohort study. *J Korean Med Sci* 2014; 29: 1226-31.
40. Kim JH, Yim JJ. Achievements in and challenges of tuberculosis control in South Korea. *Emerg Infect Dis* 2015; 21: 1913-20.
41. Kwon YS, Koh WJ. Diagnosis of pulmonary tuberculosis and nontuberculous mycobacterial lung disease in Korea. *Tuberc Respir Dis (Seoul)* 2014; 77: 1-5.
42. Koh WJ, Yu CM, Suh GY, Chung MP, Kim H, Kwon OJ, Lee NY, Chung MJ, Lee KS. Pulmonary TB and NTM lung disease: comparison of characteristics in patients with AFB smear-positive sputum. *Int J Tuberc Lung Dis* 2006; 10: 1001-7.
43. Kim YK, Hahn S, Uh Y, Im DJ, Lim YL, Choi HK, Kim HY. Comparable characteristics of tuberculous and non-tuberculous mycobacterial cavitary lung diseases. *Int J Tuberc Lung Dis* 2014; 18: 725-9.
44. Jeong YJ, Lee KS, Koh WJ, Han J, Kim TS, Kwon OJ. Nontuberculous mycobacterial pulmonary infection in immunocompetent patients: comparison of thin-section CT and histopathologic findings. *Radiology* 2004; 231: 880-6.
45. Chung MJ, Lee KS, Koh WJ, Lee JH, Kim TS, Kwon OJ, Kim S. Thin-section CT findings of nontuberculous mycobacterial pulmonary diseases: comparison between *Mycobacterium avium*-intracellulare complex and *Mycobacterium abscessus* infection. *J Korean Med Sci* 2005; 20: 777-83.
46. Lee G, Lee KS, Moon JW, Koh WJ, Jeong BH, Jeong YJ, Kim HJ, Woo S. Nodular bronchiectatic *Mycobacterium avium* complex pulmonary disease. Natural course on serial computed tomographic scans. *Ann Am Thorac Soc* 2013; 10: 299-306.
47. Lee G, Kim HS, Lee KS, Koh WJ, Jeon K, Jeong BH, Ahn J. Serial CT findings of nodular bronchiectatic *Mycobacterium avium* complex pulmonary disease with antibiotic treatment. *AJR Am J Roentgenol* 2013; 201: 764-72.
48. Koh WJ, Lee KS, Kwon OJ, Jeong YJ, Kwak SH, Kim TS. Bilateral bronchiectasis and bronchiolitis at thin-section CT: diagnostic implications in nontuberculous mycobacterial pulmonary infection. *Radiology* 2005; 235: 282-8.
49. Park HY, Suh GY, Chung MP, Kim H, Kwon OJ, Chung MJ, Kim TS, Lee KS, Koh WJ. Comparison of clinical and radiographic characteristics between nodular bronchiectatic form of nontuberculous mycobacterial lung disease and diffuse panbronchiolitis. *J Korean Med Sci* 2009; 24: 427-32.
50. Kim RD, Greenberg DE, Ehrmantraut ME, Guide SV, Ding L, Shea Y, Brown MR, Chernick M, Steagall WK, Glasgow CG, et al. Pulmonary nontuberculous mycobacterial disease: prospective study of a distinct preexisting syndrome. *Am J Respir Crit Care Med* 2008; 178: 1066-74.
51. Kartalija M, Ovrutsky AR, Bryan CL, Pott GB, Fantuzzi G, Thomas J, Strand MJ, Bai X, Ramamoorthy P, Rothman MS, et al. Patients with nontuberculous mycobacterial lung disease exhibit unique body and immune phenotypes. *Am J Respir Crit Care Med* 2013; 187: 197-205.
52. Lee AR, Lee J, Choi SM, Seong MW, Kim SA, Kim M, Chae KO, Lee JS, Yim JJ. Phenotypic, immunologic, and clinical characteristics of patients with nontuberculous mycobacterial lung disease in Korea. *BMC Infect Dis* 2013; 13: 558.
53. Marras TK, Wallace RJ Jr, Koth LL, Stulbarg MS, Cowl CT, Daley CL. Hypersensitivity pneumonitis reaction to *Mycobacterium avium* in household water. *Chest* 2005; 127: 664-71.
54. Hanak V, Kalra S, Aksamit TR, Hartman TE, Tazelaar HD, Ryu JH. Hot tub lung: presenting features and clinical course of 21 patients. *Respir Med* 2006; 100: 610-5.
55. Hahm CR, Park HY, Jeon K, Um SW, Suh GY, Chung MP, Kim H, Kwon OJ, Koh WJ. Solitary pulmonary nodules caused by *Mycobacterium tuberculosis* and *Mycobacterium avium* complex. *Lung* 2010; 188: 25-31.
56. Lim J, Lyu J, Choi CM, Oh YM, Lee SD, Kim WS, Kim DS, Lee H, Shim TS. Non-tuberculous mycobacterial diseases presenting as solitary pulmonary nodules. *Int J Tuberc Lung Dis* 2010; 14: 1635-40.
57. Jeon K, Koh WJ, Kwon OJ, Suh GY, Chung MP, Kim H, Lee NY, Park YK, Bai GH. Recovery rate of NTM from AFB smear-positive sputum specimens at a medical centre in South Korea. *Int J Tuberc Lung Dis* 2005; 9: 1046-51.
58. Kim JH, Kim YJ, Ki CS, Kim JY, Lee NY. Evaluation of Cobas TaqMan MTB PCR for detection of *Mycobacterium tuberculosis*. *J Clin Microbiol* 2011; 49: 173-6.
59. Park KS, Kim JY, Lee JW, Hwang YY, Jeon K, Koh WJ, Ki CS, Lee NY. Comparison of the Xpert MTB/RIF and Cobas TaqMan MTB assays for detection of *Mycobacterium tuberculosis* in respiratory specimens. *J Clin Microbiol* 2013; 51: 3225-7.
60. Huh HJ, Koh WJ, Song DJ, Ki CS, Lee NY. Evaluation of the Cobas TaqMan MTB test for the detection of *Mycobacterium tuberculosis* complex according to acid-fast bacillus smear grades in respiratory specimens. *J Clin Microbiol* 2015; 53: 696-8.
61. Wang HY, Bang H, Kim S, Koh WJ, Lee H. Identification of *Mycobacterium* species in direct respiratory specimens using reverse blot hybridisation assay. *Int J Tuberc Lung Dis* 2014; 18: 1114-20.
62. Huh HJ, Kwon HJ, Ki CS, Lee NY. Comparison of the genedia MTB detection kit and the cobas TaqMan MTB assay for detection of *Mycobacterium tuberculosis* in respiratory specimens. *J Clin Microbiol* 2015; 53: 1012-4.
63. Lee BH, Yoon SH, Yeo HJ, Kim DW, Lee SE, Cho WH, Lee SJ, Kim YS, Jeon D. Impact of implementation of an automated liquid culture system on diagnosis of tuberculous pleurisy. *J Korean Med Sci* 2015; 30: 871-5.
64. van Ingen J. Microbiological diagnosis of nontuberculous mycobacterial pulmonary disease. *Clin Chest Med* 2015; 36: 43-54.
65. Griffith DE, Adjemian J, Brown-Elliott BA, Philley JV, Prevots DR, Gaston C, Olivier KN, Wallace RJ Jr. Semiquantitative culture analysis during therapy for *Mycobacterium avium* complex lung disease. *Am J Respir Crit Care Med* 2015; 192: 754-60.
66. Koh WJ, Stout JE, Yew WW. Advances in the management of pulmonary disease due to *Mycobacterium abscessus* complex. *Int J Tuberc Lung Dis* 2014; 18: 1141-8.
67. Jeon K, Kwon OJ, Lee NY, Kim BJ, Kook YH, Lee SH, Park YK, Kim CK, Koh WJ. Antibiotic treatment of *Mycobacterium abscessus* lung disease: a retrospective analysis of 65 patients. *Am J Respir Crit Care Med* 2009; 180: 896-902.

68. van Ingen J, Boeree MJ, van Soolingen D, Mouton JW. Resistance mechanisms and drug susceptibility testing of nontuberculous mycobacteria. *Drug Resist Updat* 2012; 15: 149-61.
69. Bastian S, Veziris N, Roux AL, Brossier F, Gaillard JL, Jarlier V, Cambau E. Assessment of clarithromycin susceptibility in strains belonging to the *Mycobacterium abscessus* group by erm(41) and rrl sequencing. *Antimicrob Agents Chemother* 2011; 55: 775-81.
70. Choi GE, Shin SJ, Won CJ, Min KN, Oh T, Hahn MY, Lee K, Lee SH, Daley CL, Kim S, et al. Macrolide treatment for *Mycobacterium abscessus* and *Mycobacterium massiliense* infection and inducible resistance. *Am J Respir Crit Care Med* 2012; 186: 917-25.
71. Brown-Elliott BA, Vasireddy S, Vasireddy R, Iakhiaeva E, Howard ST, Nash K, Parodi N, Strong A, Gee M, Smith T, et al. Utility of sequencing the erm (41) gene in isolates of *Mycobacterium abscessus* subsp. *abscessus* with low and intermediate clarithromycin MICs. *J Clin Microbiol* 2015; 53: 1211-5.
72. Ito Y, Hirai T, Maekawa K, Fujita K, Imai S, Tatsumi S, Handa T, Matsumoto H, Muro S, Niimi A, et al. Predictors of 5-year mortality in pulmonary *Mycobacterium avium*-intracellulare complex disease. *Int J Tuberc Lung Dis* 2012; 16: 408-14.
73. Hayashi M, Takayanagi N, Kanauchi T, Miyahara Y, Yanagisawa T, Sugita Y. Prognostic factors of 634 HIV-negative patients with *Mycobacterium avium* complex lung disease. *Am J Respir Crit Care Med* 2012; 185: 575-83.
74. Kikuchi T, Kobashi Y, Hirano T, Tode N, Santoso A, Tamada T, Fujimura S, Mitsuhashi Y, Honda Y, Nukiwa T, et al. *Mycobacterium avium* genotype is associated with the therapeutic response to lung infection. *Clin Microbiol Infect* 2014; 20: 256-62.
75. Shin SJ, Choi GE, Cho SN, Woo SY, Jeong BH, Jeon K, Koh WJ. Mycobacterial genotypes are associated with clinical manifestation and progression of lung disease caused by *Mycobacterium abscessus* and *Mycobacterium massiliense*. *Clin Infect Dis* 2013; 57: 32-9.
76. Wallace RJ Jr, Brown-Elliott BA, McNulty S, Phillely JV, Killingley J, Wilson RW, York DS, Shepherd S, Griffith DE. Macrolide/Azalide therapy for nodular/bronchiectatic *Mycobacterium avium* complex lung disease. *Chest* 2014; 146: 276-82.
77. Jeong BH, Jeon K, Park HY, Kim SY, Lee KS, Huh HJ, Ki CS, Lee NY, Shin SJ, Daley CL, et al. Intermittent antibiotic therapy for nodular bronchiectatic *Mycobacterium avium* complex lung disease. *Am J Respir Crit Care Med* 2015; 191: 96-103.
78. Field SK, Fisher D, Cowie RL. *Mycobacterium avium* complex pulmonary disease in patients without HIV infection. *Chest* 2004; 126: 566-81.
79. Xu HB, Jiang RH, Li L. Treatment outcomes for *Mycobacterium avium* complex: a systematic review and meta-analysis. *Eur J Clin Microbiol Infect Dis* 2014; 33: 347-58.
80. Lee BY, Kim S, Hong Y, Lee SD, Kim WS, Kim DS, Shim TS, Jo KW. Risk factors for recurrence after successful treatment of *Mycobacterium avium* complex lung disease. *Antimicrob Agents Chemother* 2015; 59: 2972-7.
81. Min J, Park J, Lee YJ, Kim SJ, Park JS, Cho YJ, Yoon HI, Lee CT, Lee JH. Determinants of recurrence after successful treatment of *Mycobacterium avium* complex lung disease. *Int J Tuberc Lung Dis* 2015; 19: 1239-45.
82. van Ingen J, Egelund EF, Levin A, Totten SE, Boeree MJ, Mouton JW, Aarnoutse RE, Heifets LB, Peloquin CA, Daley CL. The pharmacokinetics and pharmacodynamics of pulmonary *Mycobacterium avium* complex disease treatment. *Am J Respir Crit Care Med* 2012; 186: 559-65.
83. Koh WJ, Jeong BH, Jeon K, Lee SY, Shin SJ. Therapeutic drug monitoring in the treatment of *Mycobacterium avium* complex lung disease. *Am J Respir Crit Care Med* 2012; 186: 797-802.
84. Adjemian J, Prevots DR, Gallagher J, Heap K, Gupta R, Griffith D. Lack of adherence to evidence-based treatment guidelines for nontuberculous mycobacterial lung disease. *Ann Am Thorac Soc* 2014; 11: 9-16.
85. Griffith DE, Brown-Elliott BA, Langsjoen B, Zhang Y, Pan X, Girard W, Nelson K, Caccitolo J, Alvarez J, Shepherd S, et al. Clinical and molecular analysis of macrolide resistance in *Mycobacterium avium* complex lung disease. *Am J Respir Crit Care Med* 2006; 174: 928-34.
86. Jo KW, Kim S, Lee JY, Lee SD, Kim WS, Kim DS, Shim TS. Treatment outcomes of refractory MAC pulmonary disease treated with drugs with unclear efficacy. *J Infect Chemother* 2014; 20: 602-6.
87. Jarand J, Davis JP, Cowie RL, Field SK, Fisher DA. Long term follow up of *Mycobacterium avium* complex lung disease in patients treated with regimens including clofazimine and/or rifampin. *Chest*. Forthcoming 2015.
88. Koh WJ, Hong G, Kim SY, Jeong BH, Park HY, Jeon K, Kwon OJ, Lee SH, Kim CK, Shin SJ. Treatment of refractory *Mycobacterium avium* complex lung disease with a moxifloxacin-containing regimen. *Antimicrob Agents Chemother* 2013; 57: 2281-5.
89. Lyu J, Jang HJ, Song JW, Choi CM, Oh YM, Lee SD, Kim WS, Kim DS, Shim TS. Outcomes in patients with *Mycobacterium abscessus* pulmonary disease treated with long-term injectable drugs. *Respir Med* 2011; 105: 781-7.
90. Jarand J, Levin A, Zhang L, Hui G, Mitchell JD, Daley CL. Clinical and microbiologic outcomes in patients receiving treatment for *Mycobacterium abscessus* pulmonary disease. *Clin Infect Dis* 2011; 52: 565-71.
91. Lyu J, Kim BJ, Kim BJ, Song JW, Choi CM, Oh YM, Lee SD, Kim WS, Kim DS, Shim TS. A shorter treatment duration may be sufficient for patients with *Mycobacterium massiliense* lung disease than with *Mycobacterium abscessus* lung disease. *Respir Med* 2014; 108: 1706-12.
92. Cho YJ, Yi H, Chun J, Cho SN, Daley CL, Koh WJ, Shin SJ. The genome sequence of '*Mycobacterium massiliense*' strain CIP 108297 suggests the independent taxonomic status of the *Mycobacterium abscessus* complex at the subspecies level. *PLoS One* 2013; 8: e81560.
93. Griffith DE, Brown-Elliott BA, Benwill JL, Wallace RJ Jr. *Mycobacterium abscessus*. "Pleased to meet you, hope you guess my name..." *Ann Am Thorac Soc* 2015; 12: 436-9.
94. Kim HS, Lee KS, Koh WJ, Jeon K, Lee EJ, Kang H, Ahn J. Serial CT findings of *Mycobacterium massiliense* pulmonary disease compared with *Mycobacterium abscessus* disease after treatment with antibiotic therapy. *Radiology* 2012; 263: 260-70.
95. Harada T, Akiyama Y, Kurashima A, Nagai H, Tsuyuguchi K, Fujii T, Yano S, Shigetoe E, Kuraoka T, Kajiki A, et al. Clinical and microbiological differences between *Mycobacterium abscessus* and *Mycobacterium massiliense* lung diseases. *J Clin Microbiol* 2012; 50: 3556-61.
96. Kang HK, Park HY, Kim D, Jeong BH, Jeon K, Cho JH, Kim HK, Choi YS, Kim J, Koh WJ. Treatment outcomes of adjuvant resectional surgery for nontuberculous mycobacterial lung disease. *BMC Infect Dis* 2015; 15: 76.
97. Olivier KN, Shaw PA, Glaser TS, Bhattacharyya D, Fleshner M, Brewer CC, Zalewski CK, Folio LR, Siegelman JR, Shallom S, et al. Inhaled amikacin for treatment of refractory pulmonary nontuberculous mycobacterial disease. *Ann Am Thorac Soc* 2014; 11: 30-5.

98. Rose SJ, Neville ME, Gupta R, Bermudez LE. Delivery of aerosolized liposomal amikacin as a novel approach for the treatment of nontuberculous mycobacteria in an experimental model of pulmonary infection. *PLoS One* 2014; 9: e108703.
99. Phillely JV, Wallace RJ Jr, Benwill JL, Taskar V, Brown-Elliott BA, Thakkar F, Aksamit TR, Griffith DE. Preliminary results of bedaquiline as salvage therapy for patients with nontuberculous mycobacterial lung disease. *Chest* 2015; 148: 499-506.
100. Phillely JV, Griffith DE. Treatment of slowly growing mycobacteria. *Clin Chest Med* 2015; 36: 79-90.